At page 59, line 13, please delete "108" and substitute therefor --10^8--.

At page 13, line 26, please delete ":M" and substitute therefor --mM--.

At page 13, line 27, please delete ":M" and substitute therefor --mM--.

In the Claims.

Please amend claim 1 as follows:

1. (Twice amended) A single chain antibody that specifically binds to a c-erbB2 receptor, wherein said antibody specifically binds to an epitope bound by [that is cross reactive with] F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) [at c-erbB2], and further wherein said antibody [that] is an internalizing antibody.

REMARKS

Status.

Claims 1, 3-22, 34-44, 53, and 54 are pending with entry of this amendment, no claims being cancelled and no claims being added herein. Claim 1 is amended herein. This amendment introduces no new matter and is in accordance with the Examiner's recommendation.

Oath/Declaration.

Applicants note the Examiner's assertion that the oath or declaration is still defective. A new Declaration has been prepared and is presently being executed. The new oath will be submitted when it is signed.

Information Disclosure Statement.

Applicants note that the references C40, B6, B7, and B8 were not considered because it was allegedly not clear that international search reports are publicly available. Further, the Examiner alleged "it is unclear if applicants want the entire reference including those references cited in the international search report considered."

Applicants respectfully request that the Examiner consider the search report submitted as items C40, B6, B7 and B8. With respect to the references cited therein, as the Examiner himself noted, the references cited within the search report are already of record,

cited by in the IDS, and considered by the Examiner (*see,* previous office action, page 4, line 1). Thus, Applicants simply request that the PCT written opinion be considered.

With respect to the public availability of the search report, Applicants have previously indicated that the PCT written opinion is publicly available. Moreover, it is Applicant's understanding that a reference need not be publicly available to be considered by the Examiner. For example, it is well established that copending applications, which are not public, can be made of record in an IDS and considered.

If it is the Examiner's opinion that the search report and written opinion is not prior art then Applicants respectfully request that the Examiner so indicate on the record. Otherwise, as Applicants have made the reference of record it is the Examiner's obligation to consider it.

Objections to the Specification.

The Examiner objected to the specification because the status of copending applications needed to be updated and because of the presence of certain grammatical errors. Applicants have reviewed the specification and corrected the grammatical errors as shown above.

35 U.S.C. §112, Second Paragraph.

Claims 1, 3-22, 34-44, and 53-54 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite in the recitation of the language "cross-reactive with" and in the recitation of the language "does not bind to antisera raised . . . ". Applicants respectfully traverse by argument and amendment.

Per the Examiner's recommendation, claim 1 is amended herein to recite:

> [W]herein said antibody specifically binds to an epitope bound by F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) . . .

thereby obviating the rejection of claims 1 and 3-15, and 34-44 and 54, in so far as they incorporate claim 1.

With respect to the remaining claims, Applicants submit the Examiner's rejection is improper. Contrary to the Examiner's assertion, claim 16 and associated dependent claims is not directed to an antibody necessarily used to produce an anti-idiotypic

antibody. Rather, the "anti-idiotypic antibody" language is used to further characterize the claimed antibody. More particularly, claim 16 is drawn to a **single chain** antibody that:

1) Specifically binds to a c-erbB2 receptor;

2) **When presented as an antigen**, elicits the production of an anti-idiotypic antibody that specifically binds to a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2;

3) Does not bind to antisera raised against the polypeptide set forth in SEQ ID NO: 1 and SEQ ID NO: 2, that has been fully immunosorbed with the polypeptides set forth in SEQ ID NO: 1 and in SEQ ID NO: 2.

In other words, claim 16 is directed to a single chain antibody that specifically binds c-erbB2 receptor. In accordance with item 2, above, the claimed antibody **if used to raise antisera** produces antisera cross-reactive with SEQ ID NO: 1 or 2, *i.e.,* the antibody has sufficient sequence identity SEQ ID NO: 1 or 2 to raise antisera cross-reactive with SEQ ID NO: 1 or 2. In accordance with item 3 above, requiring that the claimed antibody will not be bound by antisera raised against SEQ ID NO: 1 or 2 that is fully immunosorbed with polypeptides of SEQ ID NO: 1 or 2 requires that the antibody be **specifically cross reactive** with antisera raised against the polypeptides of SEQ ID NO: 1 or 2.

Thus, items 2 and 3 taken together require the claimed single chain antibody to be highly cross-reactive with antisera raised against polypeptides of SEQ ID NO: 1 or 2. The claimed antibody thus presents an epitope extremely similar to the epitope presented by the antibodies of SEQ ID NOS: 1 and 2.

Contrary to the Examiner's assertion, the claim is clear that the claimed antibody binds c-erbB2. It is also clear that the antibodies immunosorbed are antibodies produced in sera raised against SEQ ID NO: 1 or 2 and that once such antibodies are completely immunosorbed, the claimed antibody will not bind such antisera.

The claim is thus, definite and quite exact. The rejection of claim 16 and dependent claims, under 35 U.S.C. §112, second paragraph, is thus improper and should be withdrawn.

35 U.S.C. §112, First Paragraph.

The rejection of claims 4-13, 16-20, and 53-54, under 35 U.S.C. §112, first paragraph, was maintained and made again. In particular, the Examiner asserted that Applicants have failed to meet the enablement guidelines for an antibody that: "has a binding

affinity for c-erbB2 cells of at least 10 mM, an antibody with less than a full complement of CDRs as allegedly recited in claims 6-13, 19-20, and claims 41-42, and an antibody that specifically binds c-erB2 receptor comprising at least 10 contiguous amino acids of SEQ ID NO: 1 or SEQ ID NO: 2. More particularly the Examiner stated that t it was unclear that an antibody containing one, two or three CDRs would bind antigen as claimed or that the specification does not enable the myriad of antibodies encompassed by claim 4. Applicants respectfully traverse.

As stated in the previous Office Action, to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive

Indeed, **the Federal Circuit has expressly stated that simple screening, in particular screening of antibodies, is not undue experimentation**:

> Enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "[T]he key word is 'undue' not 'experimentation'. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the instant case, Applicants have created an antibody library comprising 7 x 10^9 members (*see, e.g.,* page 59, line 19). Clearly, Applicants have taught how to make an enormous library. The enablement question is then whether or not it is undue experimentation to obtain from that library antibodies meeting the recited limitations.

Claims 6-13 and 19-20, and 53-54.

Claims 6-13, 19-20, and 53-54 are directed to single-chain c-erbB2-bindign antibodies comprising one (*see, e.g.,* claims 6-8), or at least two (*see, e.g.,* claims 8-9), or at least three (*see, e.g.,* claim 11) complementarity determining regions of particular recited sequences. The Examiner stated that "[I]t is unclear than an antibody that contains one, two, or three CDR would bind antigen as claimed."

Applicants respectfully submit that the Examiner has mis-read the claims. The claims are not directed to antibodies **consisting of** one, or two, or three CDRs, but rather are directed to c-erbB2-binding antibodies in which one, or two or three CDRs are selected from the recited sequences. The present application and cited copending application 08/665,202"

(now U.S. Patent 5,977,322) teach that light-and/or heavy-chain shuffling can be used to increase the affinity of a single chain antibody for a particular target. Moreover, related application demonstrates the creation of anti-cerbB2 antibodies having improved affinity using light and heavy chain shuffling methods.

As illustrated in the application such shuffling can be accomplished using routine experimentation. Applicants have provided express sequences for the CDRs that are to be "held constant" in such shuffled antibodies, and, particularly in view of the data provided in the application, one of ordinary skill would appreciate that c-erbB2 binding antibodies comprising one, two or three of the recited CDRs can be produced and screened using only routine experimentation and that, by virtue of the screening/selection process such antibodies will bind to the c-erbB2 target. The application thus fully meets the requirements under 35 U.S.C. §112, first paragraph, for claims 6-13 and 19-20, and 53-54 and the rejection of these claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

Claims 4, 5, 17, 18, and 53-54.

With respect to claims 4, 5, 17, 18, and 53-54, the Examiner alleged that the specification does not enable the myriad of antibodies encompassed by claim 4 which recites an antibody that is 70% sequence identity with SEQ ID NO: 1 or 2 that would bind to the c-erbB2 on cells 10 mM. The Examiner further argued that "at this concentration there would be significant cross-reactivity with many antibodies and these antibodies would not function as claimed in claim 1.

Again, Applicants note that they have taught and exemplified the creation of an enormous antibody library having 7×10^9 members (*see, e.g.,* page 59, line 19). All that is required to prepare the antibodies of claims 4, 5, 17, 18,and 53-54 is to screen such a library for antibodies that specifically cross-react with the recited C1 or F5 antibodies and that meet the other conditions recited in the claims (*e.g.* percent sequence identity). The Federal Circuit has established that that such screening is routine experimentation. The specification is therefore fully enabling for the antibodies of claims 4, 5, 17, 18,and 53-54 and the rejection of these claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

35 U.S.C. §103(a).

Claims 1, 34-38, and 53-54 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Maier *et al.* (1991) *Cancer Res.,* 51: 5361-5369 taken with Bird *et al.*

(1988) *Science,* 242: 423-426. According to the Examiner, Maier *et al.* teaches the monoclonal antibody TA1 with is an internalizing antibody that specifically binds to the c-erbB2 receptor. Maier *et al.* does not teach a single chain antibody. Bird *et al.* is cited as teaching a single chain antibody. The Examiner finds motivation in Bird *et al.* to produce the claimed single-chain antibody. Applicants respectfully traverse.

In formulating his rejection, the Examiner improperly considered the method of making the claimed antibodies. In effect, the Examiner alleged that because **methods** to make single chain antibodies are known and full (multiple chain) anti-erbB2 antibodies are known, the particular antibodies recited in claims 1, 34-38, and 53-54 would have been obvious in light of these methods.

The courts have specifically rejected this basis for rejecting claims (*see In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1994) and *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995)). In both cases, the PTO alleged that composition claims directed to nucleic acids were obvious in view of references that taught general methods for making oligonucleotides and then using them to isolate desired nucleic acids. In *Deuel*, the Federal Circuit reversed the PTO, reasoning that:

> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

Here, as in *Bell* and *Deuel*, the Examiner improperly argues that the claimed antibodies are obvious in light of a general method for making single chain antibodies and an alleged disclosure of intact multiple-chain antibodies.

The Examiner has failed to show how the cited references provide any specific information about the particular claimed antibodies. To the contrary, as recognized by the Examiner, Maier *et al.* **fails** to disclose a single-chain anti-erbB2 antibody. The "full" antibodies disclosed by Maier *et al.* are tetramers comprising two heavy chains and two light chains joined by disulfide bonds and includes the constant (effector) region. In contrast the single chain antibodies of this invention are monomeric and do not include the constant

region. The full antibodies are so structurally different from the presently claimed single-chain antibodies that they simply fail to teach or suggest the presently claimed antibodies.

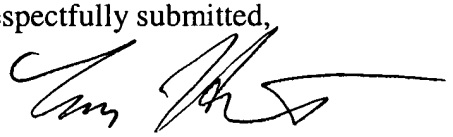
This deficiency is not remedied by Bird *et al.* To the contrary, Bird *et al.* discloses anti-BGH single chain antigen binding protein. There is no teaching or suggestion in Bird *et al.* regarding an anti-c-erbB2 antibody. The combination of Bird *et al.* and Maier *et al.* offers no molecule similar in structure to the presently claimed methods.

Since the cited ıeferences neither disclose nor suggest the existence of the particular claimed antibodies and the Federal Circuit has stated that consideration of a general method of discovery is an improper basis for an obviousness rejection, Applicants submit the Examiner has failed to make his *prima facie* case. Accordingly, the rejection of claims 1, 34-38, and 53-54 under 35 U.S.C. §103(a) should be withdrawn.

In view of the foregoing, Applicant believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415) 217-6021.

Respectfully submitted,



Tom Hunter
Attorney for Applicant(s)
Reg. No. 38,498

Encl: 1) Petition for a 3 month extension of time.

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APPENDIX I

CLAIMS PENDING IN 09/250,056 WITH ENTRY OF THIS AMENDMENT

1. (Twice amended) A single chain antibody that specifically binds to a c-erbB2 receptor, wherein said antibody specifically binds to an epitope bound by [that is cross reactive with] F5 (SEQ ID NO:1) or C1 (SEQ ID NO:2) [at c-erbB2], and further wherein said antibody [that] is an internalizing antibody.

3. The antibody of claim 1, wherein said antibody comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 1 having conservative substitutions, and SEQ ID NO: 2 having conservative substitutions.

4. (Once amended) The antibody of claim 1, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 on cells of at least 10 mM.

5. The antibody of claim 1, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

6. The antibody of claim 1, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

7. The antibody of claim 1, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 2.

8. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) of SEQ ID NO: 1.

9. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining regions (CDRs) of SEQ ID NO: 2.

10. The antibody of claim 1, wherein said antibody comprises at least two complementarity determining region (CDRs) selected from the group consisting of the complementarity determining regions of SEQ ID NO: 1, and complementarity determining regions of SEQ ID NO: 2.

11. The antibody of claim 1, wherein said antibody comprises at least three complementarity determining region (CDRs) selected from the group consisting of the complementarity determining regions of SEQ ID NO: 1, and complementarity determining regions of SEQ ID NO: 2.

12. (Once amended) The antibody of claim 11, wherein said antibody comprises three complementarity determining regions of the amino acid sequence of SEQ ID NO: 1.

13. (Once amended) The antibody of claim11, wherein said antibody [has] comprises three complementarity determining regions of the amino acid sequence of SEQ ID NO: 2.

14. (Once amended) The antibody of claim 1, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

15. (Once amended) The antibody of claim 1, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

16. (Once amended) A single chain antibody that specifically binds to a c-erbB2 receptor, said antibody comprising at least 10 contiguous amino acids from the polypeptide sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2, wherein said antibody:

when presented as an antigen, elicits the production of an anti-idiotypic antibody that specifically binds to a polypeptide comprising an amino acid sequence as set forth in SEQ ID NO: 1 or SEQ ID NO: 2; and

does not bind to antisera raised against the polypeptide set forth in SEQ ID NO: 1 and SEQ ID NO: 2, that has been fully immunosorbed with the polypeptides set forth in SEQ ID NO: 1 and in SEQ ID NO: 2.

17. (Once amended)The antibody of claim 16, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 on cells of at least 10 mM.

18. The antibody of claim 16, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

19. The antibody of claim 16, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

20. The antibody of claim 16, wherein said antibody comprises a complementarity determining region of SEQ ID NO: 2.

21. (Once amended) The antibody of claim 16, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

22. (Once amended) The antibody of claim [1]16, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

34. A chimeric molecule that specifically binds a cell bearing a c-erbB-2, said chimeric molecule comprising an effector molecule attached to an antibody of claims 1 or 16.

35. The chimeric molecule of claim 34, wherein said effector is selected from the group consisting of a cytotoxin, a label, a radionuclide, a drug, a liposome, a ligand, and an antibody.

36. The chimeric molecule of claim 34, wherein said chimeric molecule is a fusion protein.

37. The chimeric molecule of claim 34, wherein said cell is a cancer cell.

38. The chimeric molecule of claim 37, wherein said cancer cell is a breast cancer cell.

39. (Once amended) The chimeric molecule of claim 34, wherein said antibody shares at least 70% sequence identity with the amino acid sequence of SEQ ID NO: 1or SEQ ID NO: 2 and wherein said antibody has a binding affinity for c-erbB2 of at least 10 mM.

40. The chimeric molecule of claim 34, wherein the amino acid sequence of said antibody differs from the amino acid sequence of SEQ ID NO: 1 or SEQ ID NO: 2 by no more than 30 residues.

41. The chimeric molecule of claim 34, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 1.

42. The chimeric molecule of claim 34, wherein said antibody comprises a complementarity determining region (CDR) of SEQ ID NO: 2.

43. (Once amended) The chimeric molecule of claim 34, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 1.

44. (Once amended) The chimeric molecule of claim 34, wherein said antibody comprises the amino acid sequence of SEQ ID NO: 2.

53. (Once amended) A composition comprising a pharmacological excipient and the antibody of claims 1 or 16

54. (Once amended) A composition comprising a pharmacological excipient and the chimeric molecule of claim 34.